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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003904201 for a patent by BARRY JOHN ALLEN as filed on 11 August 2003.

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Twenty-seventh day of September 2004

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PROVISIONAL PATENT SPECIFICATION

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Invention Title
The alpha-conjugate of the monoclonal antibody c595 for therapy of pancreatic, prostate and other cancers.

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The invention relates to an improved adjunctive therapy for early stage metastatic cancer, or cancer at the minimum residual disease stage..

The unique aspects of the invention is the combination of an alpha emitting radioisotopes (RI) (Tb-149, At-211, Bi-212, Bi-213) with monoclonal antibodies (mab) against the MUC-1 receptor, which allows the killing of individual cancer cells with the highest possible efficacy. These radioimmunoconjugates (RIC) have never been produced before.

The essential elements and advantages of the invention are:

Stable bonding of the alpha emitting radioisotope (RI) via chelators to monoclonal antibodies.

Monoclonal antibody c595 has high selectivity to cancer cells as MUC-1 is highly expressed on many cancer cells.

Alpha radiation kills cancer cells in 2-3 nuclear hits.

Alpha radiation spares capillary endothelial cells.

Half-life is suitable for preparation and the stability of the RIC.

Short half-life is suitable for killing of isolated cancer cells and preangiogenic lesions.

Low concomitant radiation dose to normal tissue.

High therapeutic ratio.

Prognosis for survival should be improved by treatment of micrometastases in subclincial, early stage metastatic disease or at the minimum residual disease stage.

The invention therefore overcomes the following deficiencies in prior art proposals:

Radiocolloid therapy is not suitable for adjunctive therapy as it is not selective of cancer cells.

Beta and gamma emitting radionuclides have been coupled to specific monoclonal antibodies against cancer cells. However, because most of the radiation dose leaves the cancer cell, therapeutic doses cannot be achieved without severe complications.

Chemotoxins affect single cells. The range of the emitted alpha particles are three to five times the diameter of a cancer cell, so the radiation dose is specific to small clusters of cancer cells.

The Invention

Production of alpha-emitting radionucklides The rare earth nuclide 149Tb is produced on a tandem, cyclotron or linear accelerator using high energy heavy ions such as boron or carbon or nitrogen ions to bombard targets of Praseodymium, eg Pr(12C,4n) or Neodymium Nd(12C,5n) or at GeV energies using proton induced spallation. At-211 is produced with 26 MeV alphas bombarding a Bi target. Bi-213 is available from the decay of the parent radioisotope Ac-225, or from proton bomdardment of Ra-226. Bi-212 is available from the decay of the parent radioisotope Th-228.

Purification The product nuclides are separated from the thick target by dissolution in 6M nitric acid, the sample is irradiated to dryness and yield determined by gamma ray spectroscopy. The residue is dissolved in 0.16 M _hydroxyisobutyric acid and passed through a cation exchange column (particle size 13 µm). The pH of the eluent is adjusted to 5 by aqueous ammonia. Elution was under a pressure of 7 kg cm-2 at a flow rate of 0.5 mL min-1. Terbium fractions are dried gently and heated to 450 degrees to destroy the Tb-isobutyrate complex. The residue is dissolved in dilute nitric or hydrochloric acid for the radiolabelling procedure. The Bi-212,213 are eluted from the parent RI with hydroiodic acid.

Labeling The purified product is chelated to the monoclonal antibody c595, which targets the backbone of the MUC-1 receptor expressed on prostate, pancreatic and other cancer cells. A number of different chelation procedures are available which use cDTPA, DOTA and TETA to produce the alpha-immunoconjugate (AIC).

Results We have produced the Tb-149 and Bi-213-AICs, and tested the labelling efficiency with prostate, pancreatic and other cancers (>90%), in vitro cell survival and in vivo biodistribution in nude mice with tumour xenografts.
The synthesis of the Bi-213 labelled anti-MUC-1 mab c595 is specifically protected by this application.

Clinical Protocol High risk patients would be treated with the AIC immediately after detection and removal of the primary tumour to selectively kill isolated cancer cells or small nests of such cells at the preangiogenic stage, where rapid uptake and incorporation can occur. Concomitant dose to normal tissue is much lower than for beta radionuclides, and improved prognosis is envisaged.

Background

Date of conception of alpha therapy 1 October 1992
Date of first drawing, sketch or prototype 2 May 2002

Details of disclosures
Numerous papers have now been published about alpha therapy with labeled monoclonal antibodies. However, the concept of using the MUC1 as a target, c595 as the targeting vehicle, and Bi-213 the alpha-emitting radiolabel, has not been explored as yet.

Experience with B(n,alpha) therapy, alpha therapy with labeled monoclonal antibodies, microdosimetry of high LET radiation led to the development of this new approach.

General field of invention
Nuclear Medicine and Radiation Oncology

The problem solved by the invention
Adjuvent therapy of subclinical disease to eliminate micrometastatic disease at the subclinical stage.

Prior Art

Monoclonal antibodies can target antigens on the membranes of cancer cells.
Beta emitting radio-immunoconjugates with I-131, In-111, Y-90 etc have been synthesized but are relatively ineffective in therapy.
Chemotherapy drugs are a systemic therapy but mostly are incapable of eliminating the disease.
Alpha emitting radioisotopes have been shown to be effective in killing isolated cells and pre-angiogenic lesions.